"Exploring the role and therapeutic potential of sex hormone binding globulin (SHBG) in the course of insulin resistance, inflammation, lipotoxicity in adipose stem progenitor cells and adipocytes in equine metabolic syndrome (EMS) mares"

In recent years, equine metabolic syndrome (EMS) prevalence has rapidly increased due to permanent overfeeding of animals with non-structural carbohydrates (NSC) combined with reduce physical activity. EMS horses are characterized by specific phenotype which includes obesity, regional adiposity and insulin resistance. However as recently showed, even non-obese horses might suffer for EMS, which highlights complexity of disease. What is more, it was thought that EMS usually affects primitive breeds of horses and ponies, but as recently showed, also sport horses, threatening their sport careers. Currently, beside caloric restrictions and increased physical activity, there are no effective strategies to manage EMS. Therefore, there is strong need to develop effective pharmacological therapy for EMS, since so far such treatment does not exists.

Bearing in mind our previous intensive research related to EMS and data from other Authors, we believe that effective pharmacological therapy in the course of EMS should be targeted at metabolic remodeling of adipose tissue and subpopulations of resident progenitor cells (ASCs). Recently, it has been shown that in adipose reside ASC subpopulations with distinct metabolic features, with the phenotype $CD34^{high}$, $CD34^{low}$,$CD34^{-}$ and cells regulating adipogenesis called Aregs, which can greatly regulate inflammation of the adipose tissue, its insulin resistance and lipotoxicity. Interestingly, studies have shown, that females are more prone for metabolic syndrome development than males, due to their endocrine predispositions. Our preliminary data confirms that phenomenon, since we have found, that in EMS mares, both systemic and SAT concentration of sex hormone binding globulin (SHBG) are seriously reduced. SHBG is a protein found primarily in the liver and is responsible for transporting sex hormones to target cells. Importantly, our team first demonstrated its presence in adipose tissue and ASC, but we still do not know the exact molecular mechanism of SHBG in these cells. Recent studies indicated, that the systemic level of SHBG is closely correlated with the development of metabolic syndrome, obesity and type II diabetes in humans and its increased levels ameliorates insulin resistance. Our research has also shown its relationship with the development of EMS.

Therefore, as part of the proposed project, we believe that systemic administration of SHBG in mares suffering from EMS will reverse negative metabolic changes in fat tissue including inflammation, insulin resistance and lipotoxicity. We believe, that SHBG as a result of its systemic application may modulate the metabolism of adipocytes and ASCs and their subpopulations as well as activate adipose-residing regulatory T-lymphocytes (TREGs) and thereby increase the anti-inflammatory capacity of adipose tissue and increase its insulin sensitivity, which in turn will contribute for EMS treatment. Moreover, we hypothesized, that systemic administration of SHBG will modulate adipogenic differentiation potential of ASCs as well as their subtypes through reduction of activity of two important long non coding RNA (lncRNA) i.e. ASMER 1 and 2. In addition, we plan to investigate polymorphism and methylation of the SHBG gene, which may be significantly involved in the pathophysiology of EMS. Currently, apart from the rodent research model that shows SHBG expression only in the liver, there is no other human-like research model. Horses, similarly to humans, are characterized by SHGB expression not only in the liver but also in adipose tissue, which makes our horse model unique on a global scale.

Drug treatment for mares suffering from the metabolic syndrome using SHBG may become an effective EMS treatment strategy, giving hope to the recovery of thousands of horses suffering worldwide.